Turning Tundra Tumor into a Destination Brimming with Hungry T-cells

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NIH NATIONAL CANCER INSTITUTE

Tundra vs. tropical island

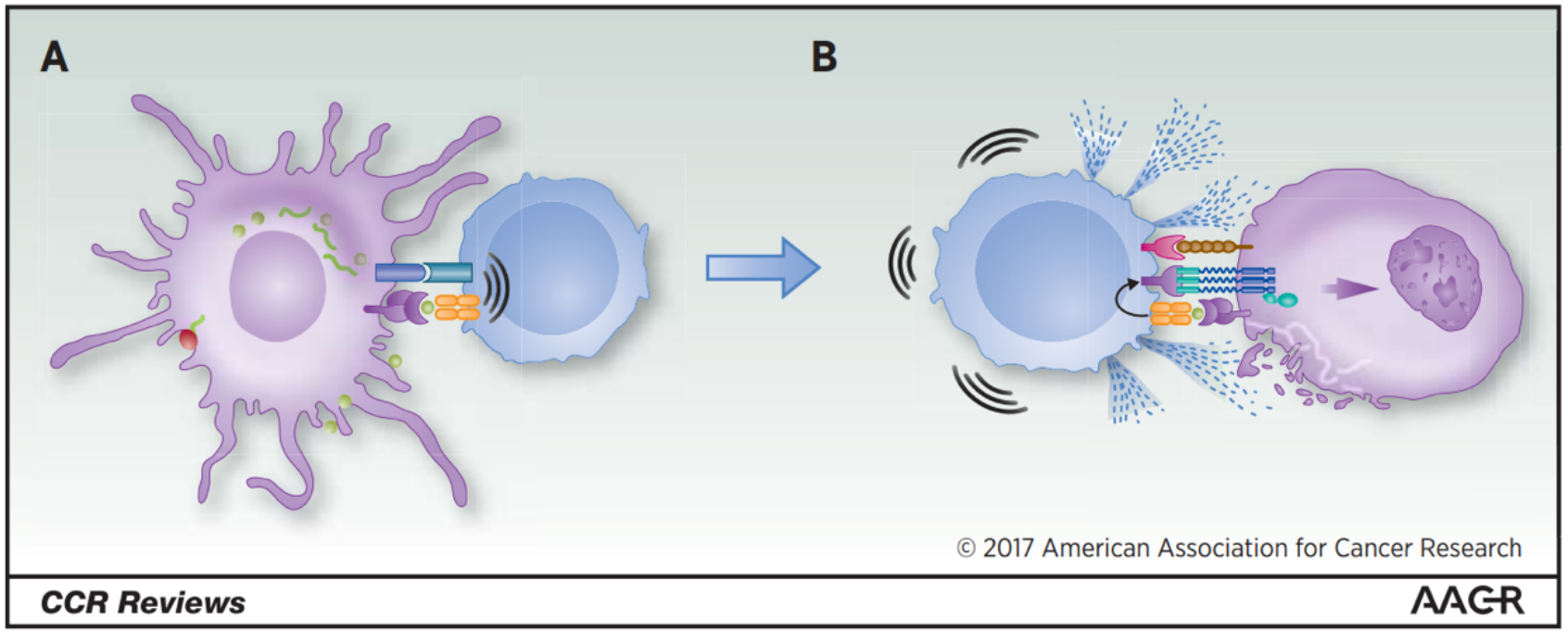
Barren, cold
Tumor: No T-cells

Teeming with life, hot
Tons of activated T-cells

Requirements for Effective Immunotherapy

Generation of Immune Response
"Initiation"

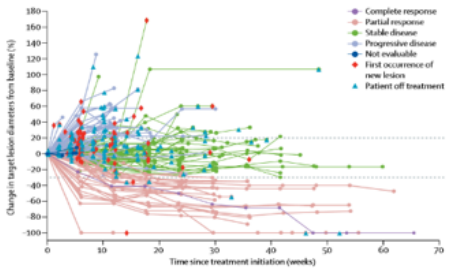
Functional Effector Cells within the Tumor
"Facilitation"



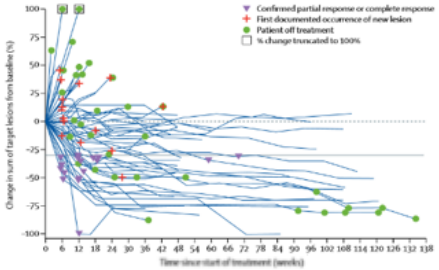
Bilusic M, Madan RA, Gulley JL *Clin Ca Res* 2017

PD-1/PD-L1 inhibition

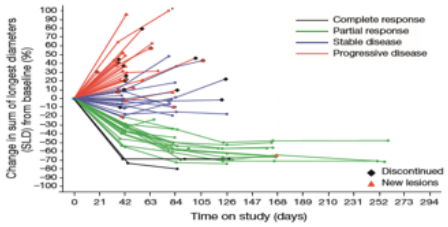
Rapid, deep, durable responses
Across a wide range of tumors
Seen in a subset of patients
Not seen in #ProstateCancer



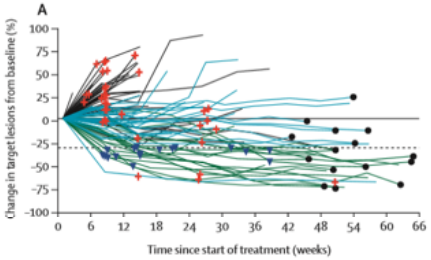
NSCLC: avelumab
Gulley JL et al. Lancet Oncol 2017



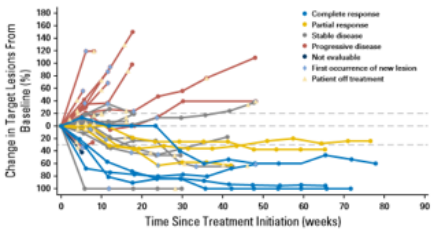
MSI hi CRC: nivolumab
Overman MJ et al. Lancet Oncol 2017



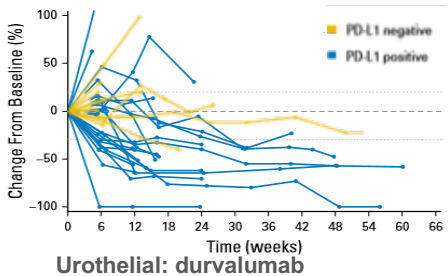
Urothelial: atezolizumab
Powles T et al. Nature 2014



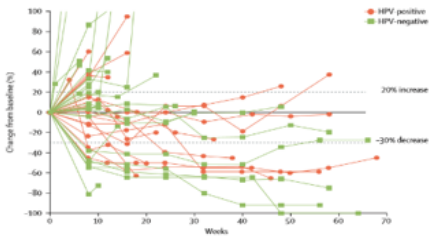
NSCLC (squamous only): nivolumab
Rizvi NA et al. Lancet Oncol 2015



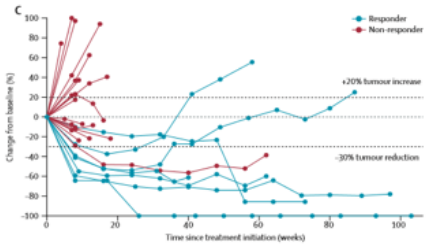
Urothelial: avelumab
Apolo AB et al. J Clin Oncol 2017



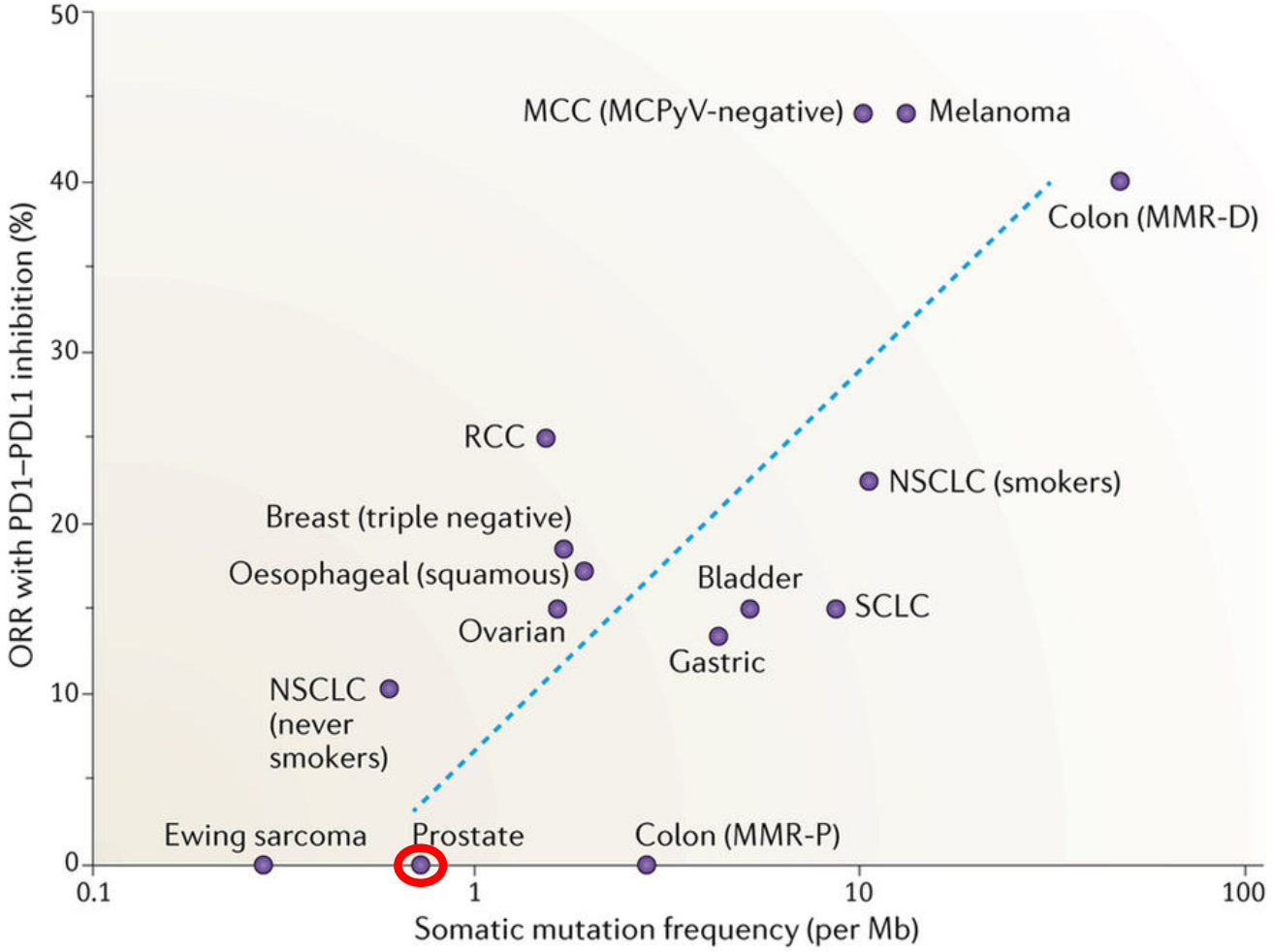
Urothelial: durvalumab
Massard C et al. JCO 2016



HNSCC: pembrolizumab
Seiwert TY et al. Lancet Oncol 2016



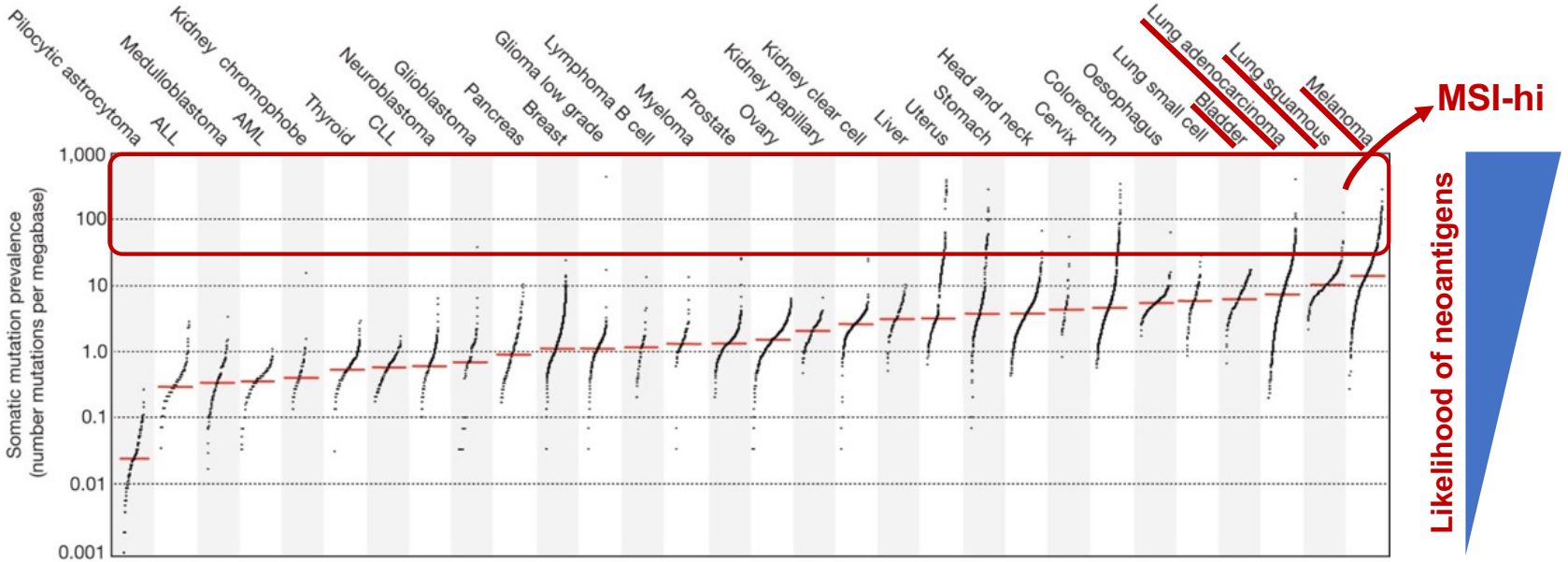
Urothelial: pembrolizumab
Plimack ER P et al. Lancet Oncol 2017



Yarchoan et al., 2017

Nature Reviews | Cancer

The prevalence of somatic mutations across human cancer types



T-cell-poor?
Target self antigens → vaccine

T-cell-inflamed?
Target neoantigens

Alexandrov LB et al. Nature 2013;500:415–21.

nature

MSI Hi Prostate Cancer

- Approval with pembrolizumab
- Incidence
  - Localized PC ~2%
  - Autopsy series of mCRPC ~12%
    - Pritchard et al., *Nature Com* 2014
  - Ongoing testing suggests 5-6% of mCRPC
- Suggests all patients with mCRPC should be tested

Pembrolizumab Response Rate by Tumor Type.*

Tumor Type	No. of Tumors	Patients with a Response	Range of Response Duration
		no. (%)	*mo*
Colorectal cancer	90	32 (36)	1.6+ to 22.7+
Endometrial cancer	14	5 (36)	4.2+ to 17.3+
Biliary cancer	11	3 (27)	11.6+ to 19.6+
Gastric or gastroesophageal junction	9	5 (56)	5.8+ to 22.1+
Pancreatic cancer	6	5 (83)	2.6+ to 9.2+
Small-intestine cancer	8	3 (38)	1.9+ to 9.1+
Breast cancer	2	2 (100)	7.6 to 15.9
Prostate cancer	2	1 (50)	9.8+
Other cancers	7	3 (43)	7.5+ to 18.2+

* Response was as defined by RECIST. "Other cancers" includes one patient each with the following tumor types: bladder, esophageal, sarcoma, thyroid, retroperitoneal, small-cell lung cancer, and renal cell cancer (includes two patients who could not be evaluated and were considered not to have had a response). A + sign indicates that the response was ongoing at the time of data cutoff.

Lemery et al., *NEJM* 2017

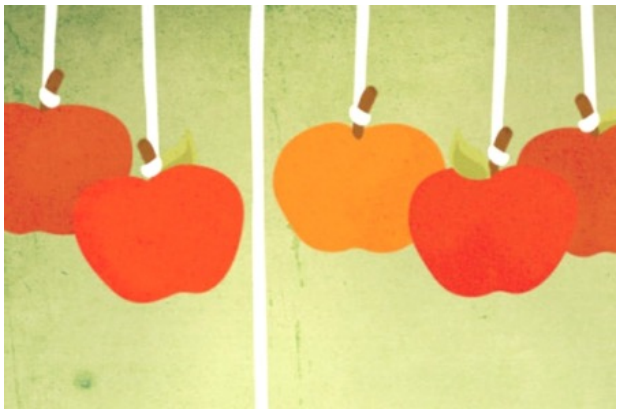
Easy Pickin’ is Over

What's left?

Immune Recognition*	Clinical Response to ICI +
+	Melanoma Lung Bladder
-	N/A

*In part based on recognition of immune relevant mutations

What's left?

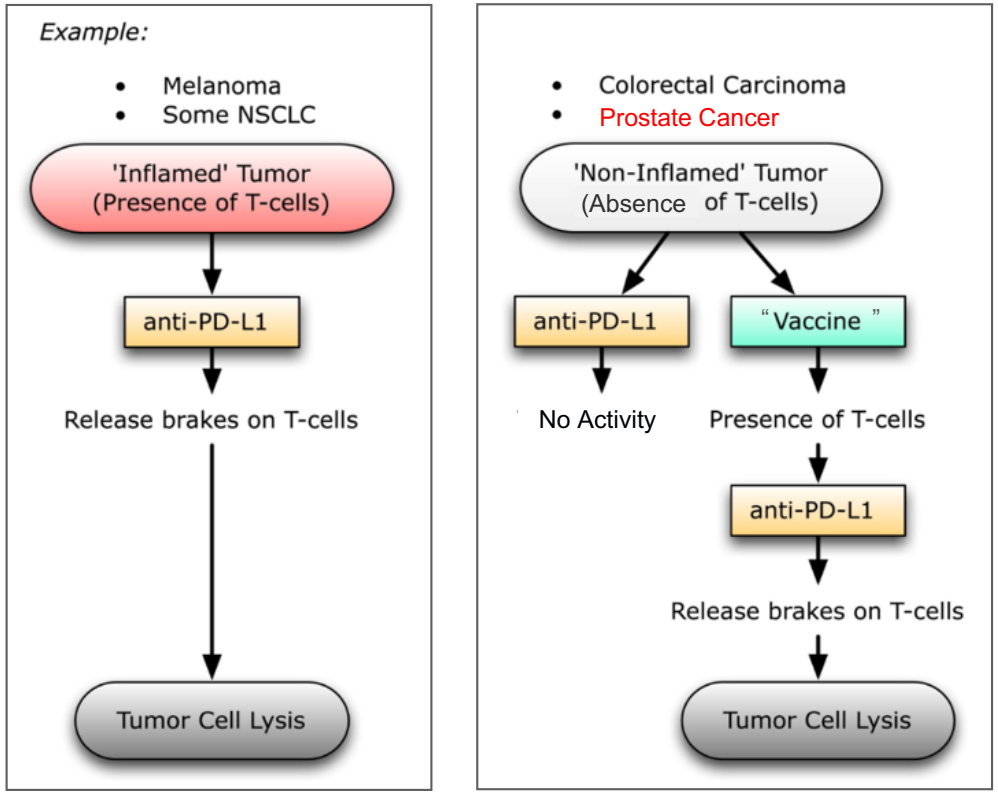


Immune Recognition*	Clinical Response to ICI +	Clinical Response to ICI -
+	Melanoma Lung Bladder	Primary Refractory Acquired Resistance
-	N/A	Prostate Breast CRC Pancreatic

-Next frontier
-Will require combination therapy strategies

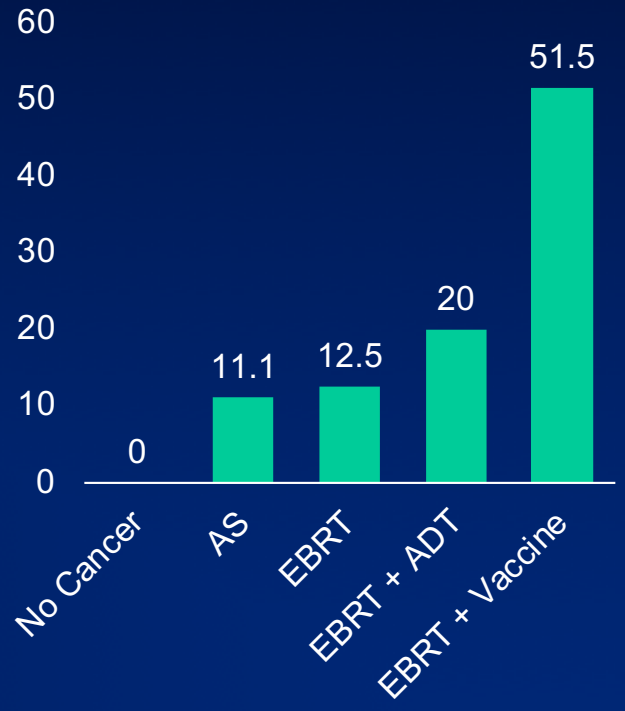
*In part based on recognition of immune relevant mutations

Working Model for T-cell infiltration and Immunotherapy Implications



Anti-tumor Immune Response More Efficient with Vaccine (Prostvac) vs. SOC

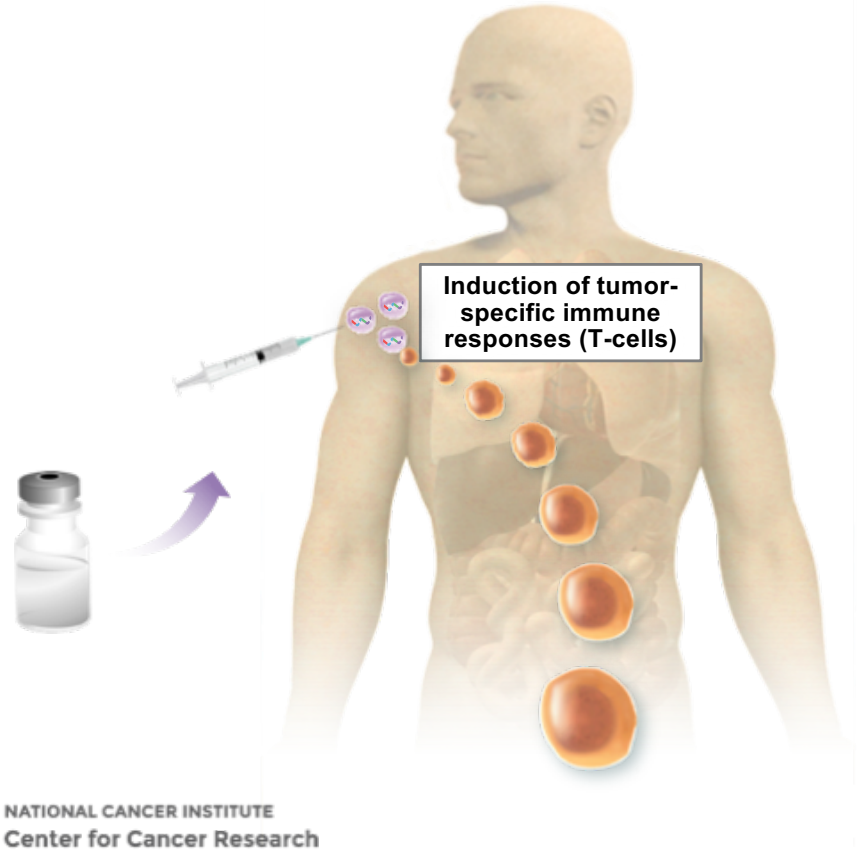
	Cancer-free controls (n = 15)	AS (n = 9)	EBRT (no vaccine; n = 8)	EBRT + ADT (n = 15)	EBRT+ Vaccine (n = 33)
Western blot	0 (0%)	1 (11.1%)	1 (12.5%)	3 (20.0%)	15 (45.5%)
Antigen array	0 (0%)	1 (11.1%)	0 (0%)	2 (13.3%)	7 (21.2%)
Overall	0 (0%)	1 (11.1%)	1 (12.5%)	3 (20.0%)	17 (51.5%)



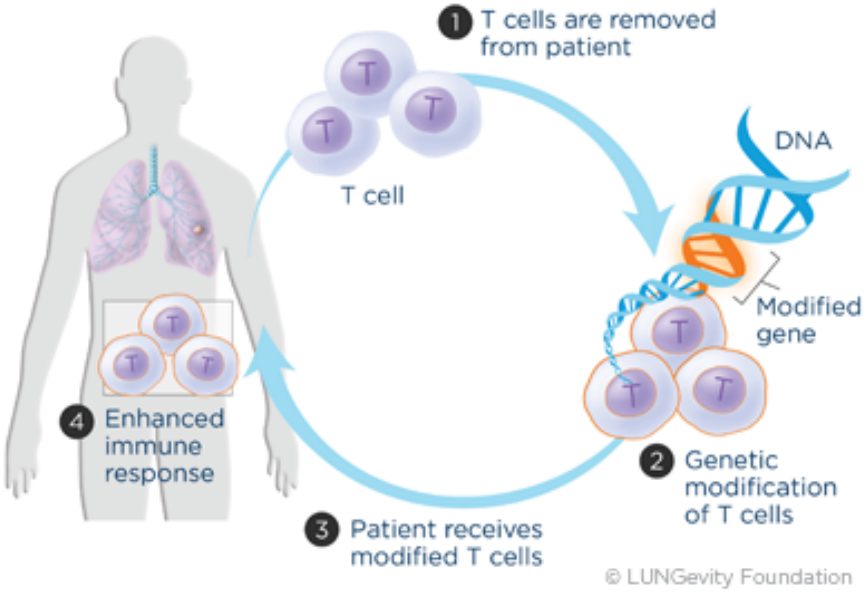
Nesslinger… Schlom, Gulley et al, *Clin Ca Res*, 2010

Developing T-cells to fight

Therapeutic Vaccine



Adoptive Cellular Therapy (ACT)



What is sufficient to initiate an immune response?

	ICI only	Vaccine		ACT	
	No Ag	Self Ag	Neo Ag	Self Ag	Neo Ag
Logistics	simple				
Needs hot tumor	Yes				
Immunogenicity	N/A				
Target Selection	N/A				

What is sufficient to initiate an immune response?

	ICI only	Vaccine		ACT	
	No Ag	Self Ag	Neo Ag	Self Ag	Neo Ag
Logistics	simple	simple	complex	complex	complex
Needs hot tumor	Yes	No		No	
Immunogenicity	N/A				
Target Selection	N/A				

What is sufficient to initiate an immune response?

	ICI only	Vaccine		ACT	
	No Ag	Self Ag	Neo Ag	Self Ag	Neo Ag
Logistics	simple	simple	complex	complex	complex
Needs hot tumor	Yes	No		No	
Immunogenicity	N/A	weak	strong	variable*	
Target Selection	N/A				

*Typically only 1 target rather than potential for multiple targets / epitopes in a vaccine. TCR Catch Bond

How to initiate an immune response

	ICI only	Vaccine		ACT	
	No Ag	Self Ag	Neo Ag	Self Ag	Neo Ag
Logistics	simple	simple	complex	complex	complex
Needs hot tumor	Yes	No		No	
Immunogenicity	N/A	weak	strong	variable*	
Target Selection	N/A	Immune System		Scientists	

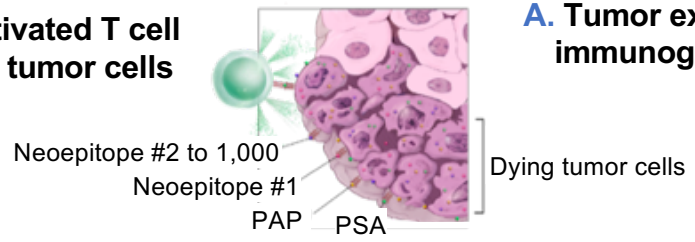
*Typically only 1 target rather than potential for multiple targets / epitopes in a vaccine. TCR Catch Bond

Do you need to target a neo-antigen to get a high avidity immune response?

Antigen spreading and the tumor immunity cycle

E. **Fully activated T cell destroys tumor cells**

A. **Tumor expresses different immunogenic targets**

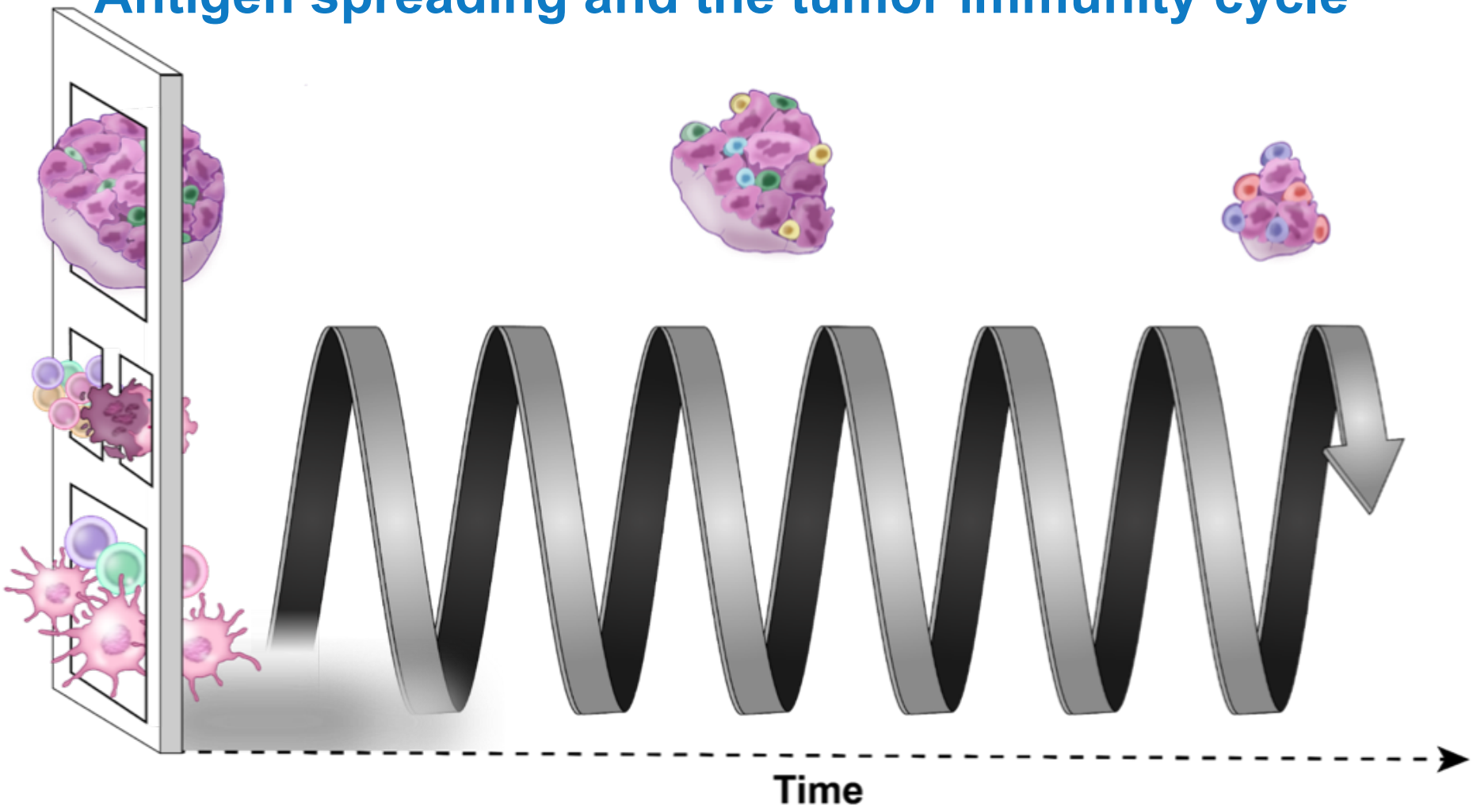


D. **Newly activated tumor-specific T cells form in greater concentration and variation**

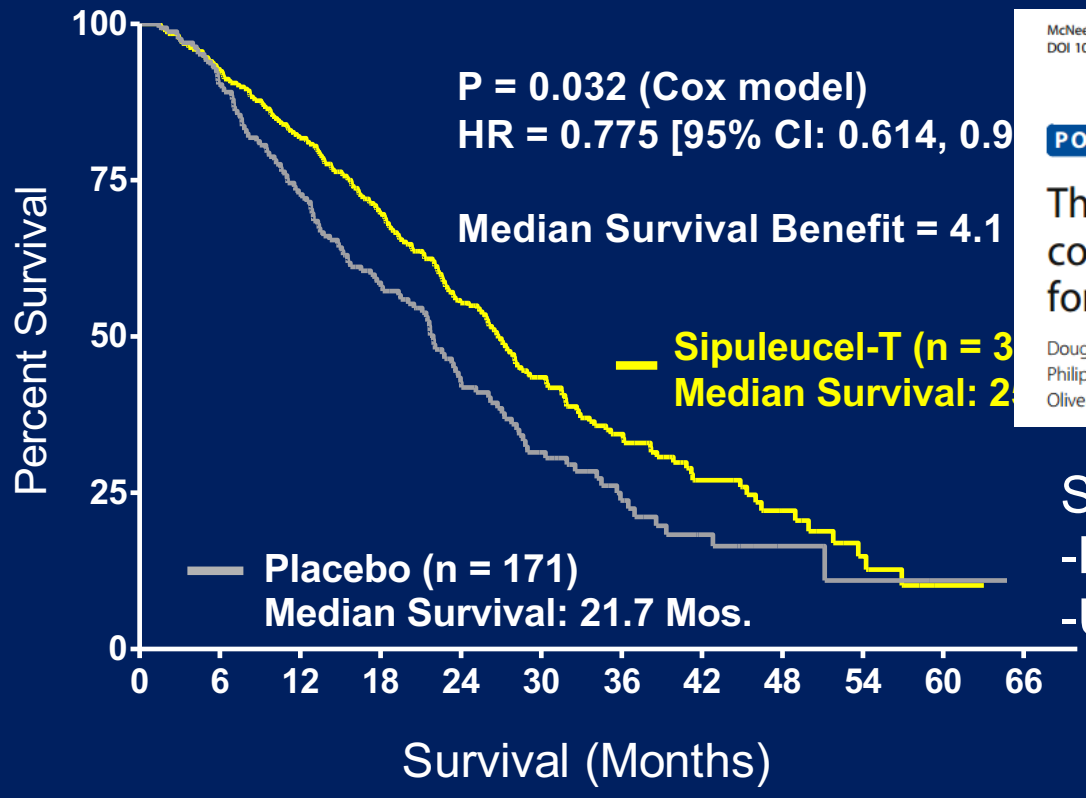
B. **Dendritic cell phagocytoses tumour cell along with a transfer of tumor-specific antigens**

C. **Mature dendritic cell presents tumor-specific antigens to T cells**

Antigen spreading and the tumor immunity cycle



Sipuleucel-T: IMPACT trial



Kantoff et al., NEJM 2010

McNeel et al. Journal for ImmunoTherapy of Cancer (2016) 4:92
DOI 10.1186/s40425-016-0198-x

Dec 2016

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES Open Access

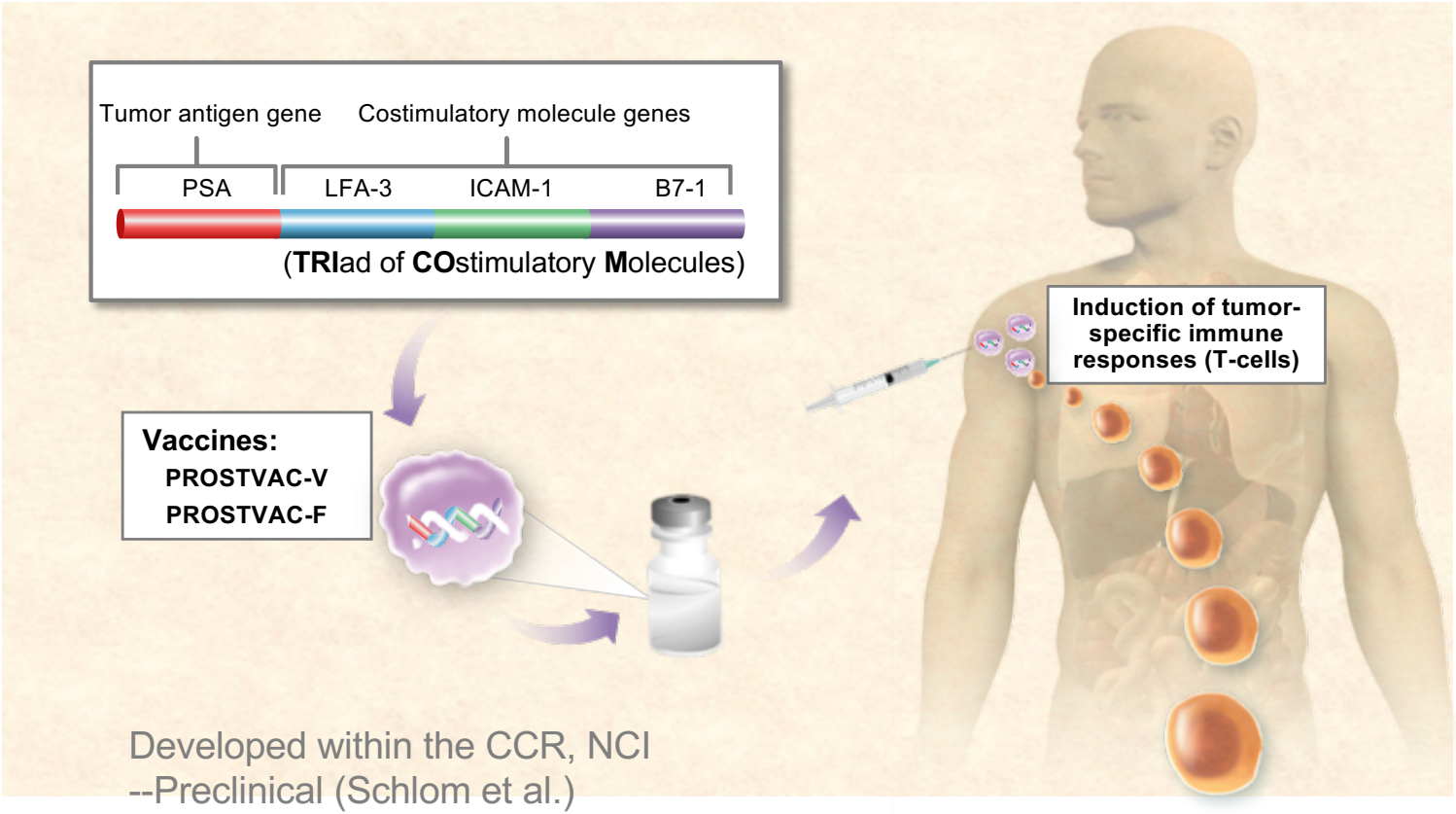
The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of prostate carcinoma

Douglas G. McNeel[1], Neil H. Bander[2], Tomasz M. Beer[3], Charles G. Drake[4], Lawrence Fong[5], Stacey Harrelson[6], Philip W. Kantoff[7], Ravi A. Madan[8], William K. Oh[9], David J. Peace[10], Daniel P. Petrylak[11], Hank Porterfield[12], Oliver Sartor[13], Neal D. Shore[6], Susan F. Slovin[7], Mark N. Stein[14], Johannes Vieweg[15] and James L. Gulley[16*]

Sipuleucel-T
-Don't expect PSA decrease or OR
-Use early, in less aggressive disease

PROSTVAC-VF

Proposed Mode of Action



Developed within the CCR, NCI
--Preclinical (Schlom et al.)
--Clinical (Gulley et al.)

NIH Medical Arts and Photography

Research Article

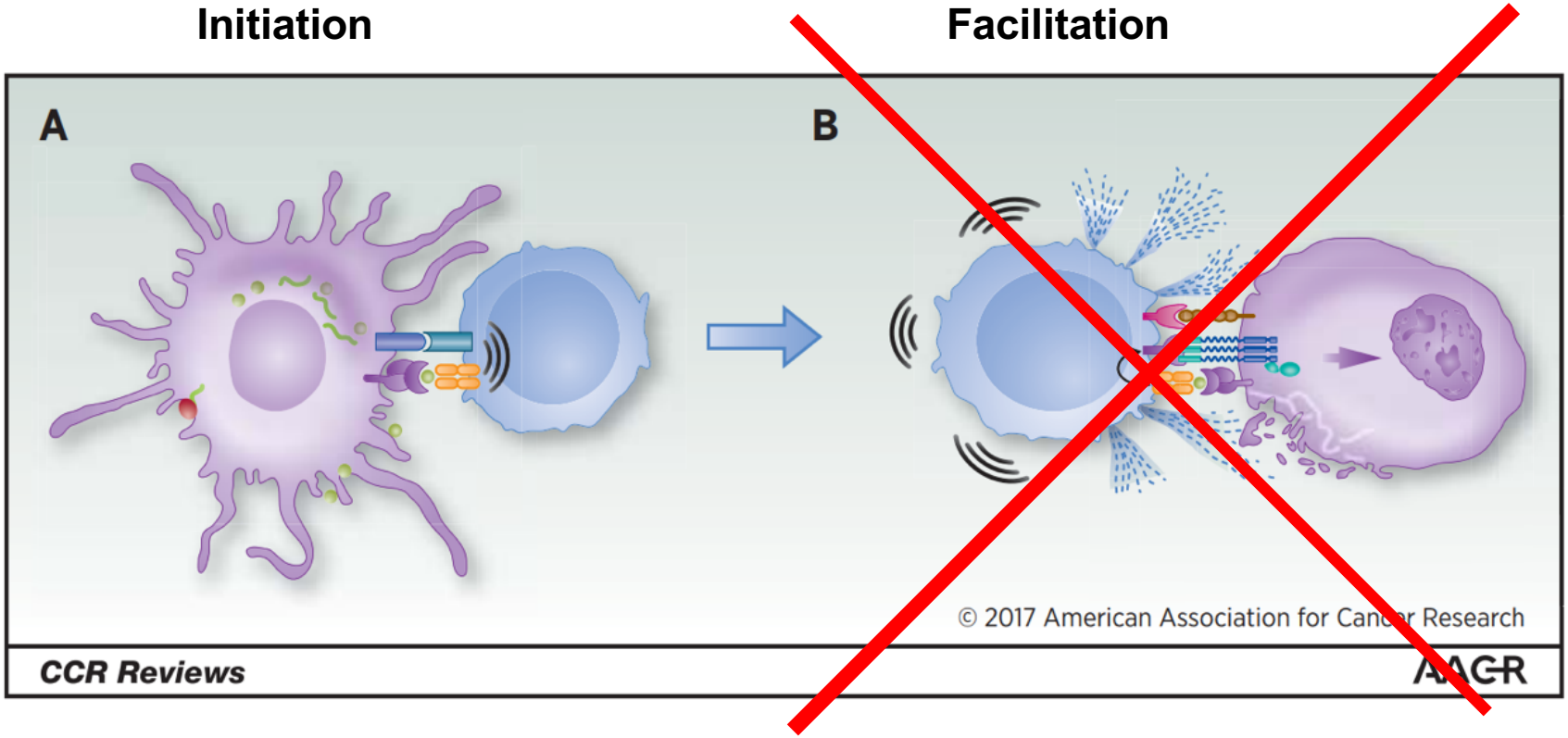
Cancer Immunology Research

Immune Impact Induced by PROSTVAC (PSA-TRICOM), a Therapeutic Vaccine for Prostate Cancer

James L. Gulley[1], Ravi A. Madan[1], Kwong Y. Tsang[1], Caroline Jochems[1], Jennifer L. Marté[1], Benedetto Farsaci[1], Jo A. Tucker[1], James W. Hodge[1], David J. Liewehr[2], Seth M. Steinberg[2], Christopher R. Heery[1], and Jeffrey Schlom[1]

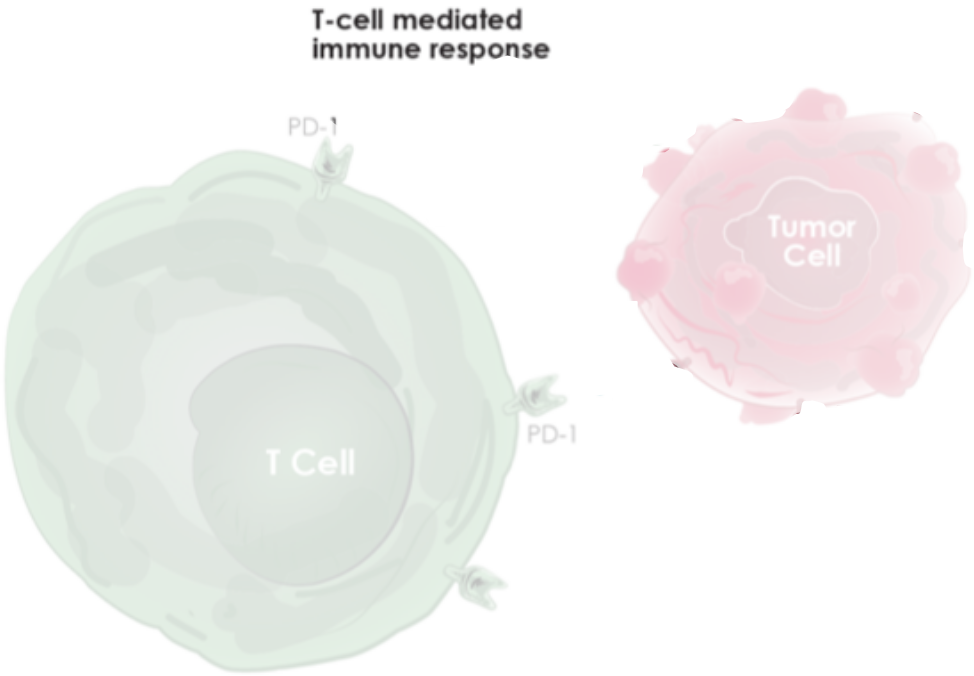
Test	Result	Comment
PSA Specific Immune response	56.7% (59/104)	28 days after last vaccine
--Median fold increase in PSA specific immune response	5X	# of PSA specific T-cells identical to flu T-cells
Antigen Spreading	67.9% (19/28)	
Anti-PSA Ab	0.57% (2/349)	

Requirements for Effective Immunotherapy



Bilusic M, Madan RA, Gulley JL *Clin Ca Res* 2017

Importance of PD-1/PD-L1 blockade



NIH. News Headlines: https://ccr.cancer.gov/news/article/investigators-lead-first-human-trials-of-new-immunotherapy-drug (accessed August 2017)

Prostvac + Ipi or Nivo or Comb.

Patient Population: Localized Prostate Cancer, candidates for RP

Cohort 1: Vaccine + Ipi + Nivo (n=10, mCRPC)

Cohort 2: Vaccine + Nivo (n=16)

Cohort 3: Vaccine + Ipi (n=16)

Cohort 4: Vaccine + Ipi + Nivo (n=16)

Baseline	Week 0	Week 2	Week 5	Week 8	Week 9
Biopsy	Prostvac-V	Prostvac-F	Prostvac-F	Prostvac-F	RP
		Ipilimumab	**Ipilimumab**	**--**	
		Nivolumab	**Nivolumab**	**Nivolumab**	

Ipilimumab 1 mg/kg, Nivolumab 240 mg

(NCT02933255) PI Gulley

Prostvac + Ipi or Nivo or Comb.

Patient Population: Localized Prostate Cancer, candidates for RP

Cohort 1: Vaccine + Ipi + Nivo (n=10, mCRPC)

Cohort 2: Vaccine + Nivo (n=16)

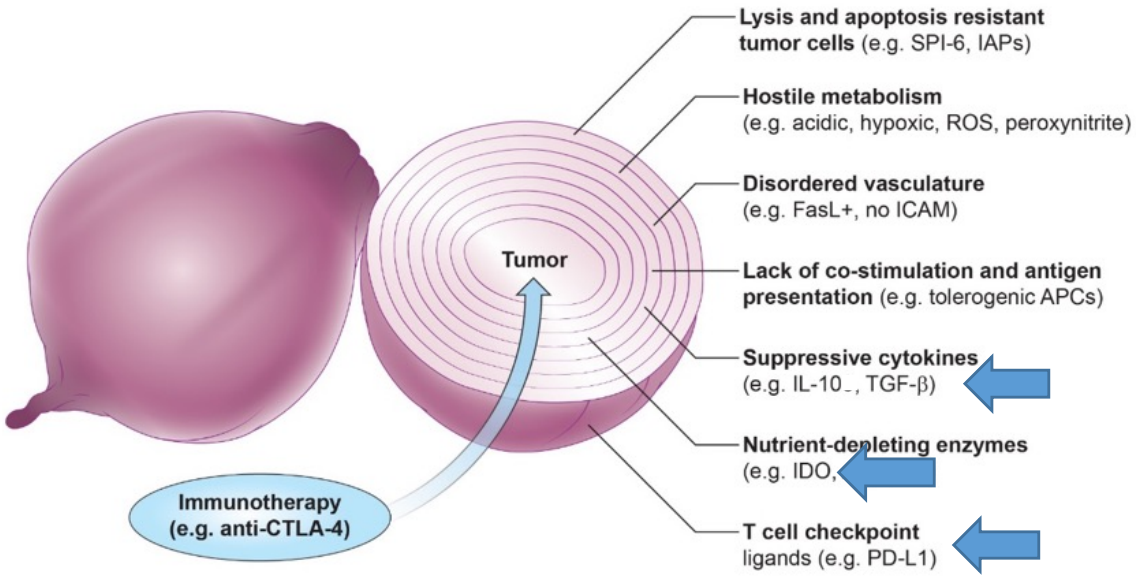
~~Cohort 3: Vaccine + Ipi (n=16)~~

~~Cohort 4: Vaccine + Ipi + Nivo (n=16)~~

Primary analysis: Immune infiltrate by IHC
Secondary: Safety
Imaging
Peripheral immune analysis
**In depth analysis of change in tumor microenvironment post immunotherapy
-RNA Seq, multiplex IF, TCR Seq, NGS assays for MSI etc.

(NCT02933255) PI Gulley

Multi-layered immunosuppression



- Tumors insulate themselves with dense layers of immunosuppressive stroma
- Overcoming the many layers of interconnected and often functionally redundant immune suppressive mechanisms represents a daunting challenge for tumor-specific T cells
- Immunotherapy can "peel back" the layers of local immune suppression, thereby restoring the capacity of T cells to eradicate the tumor

sitc

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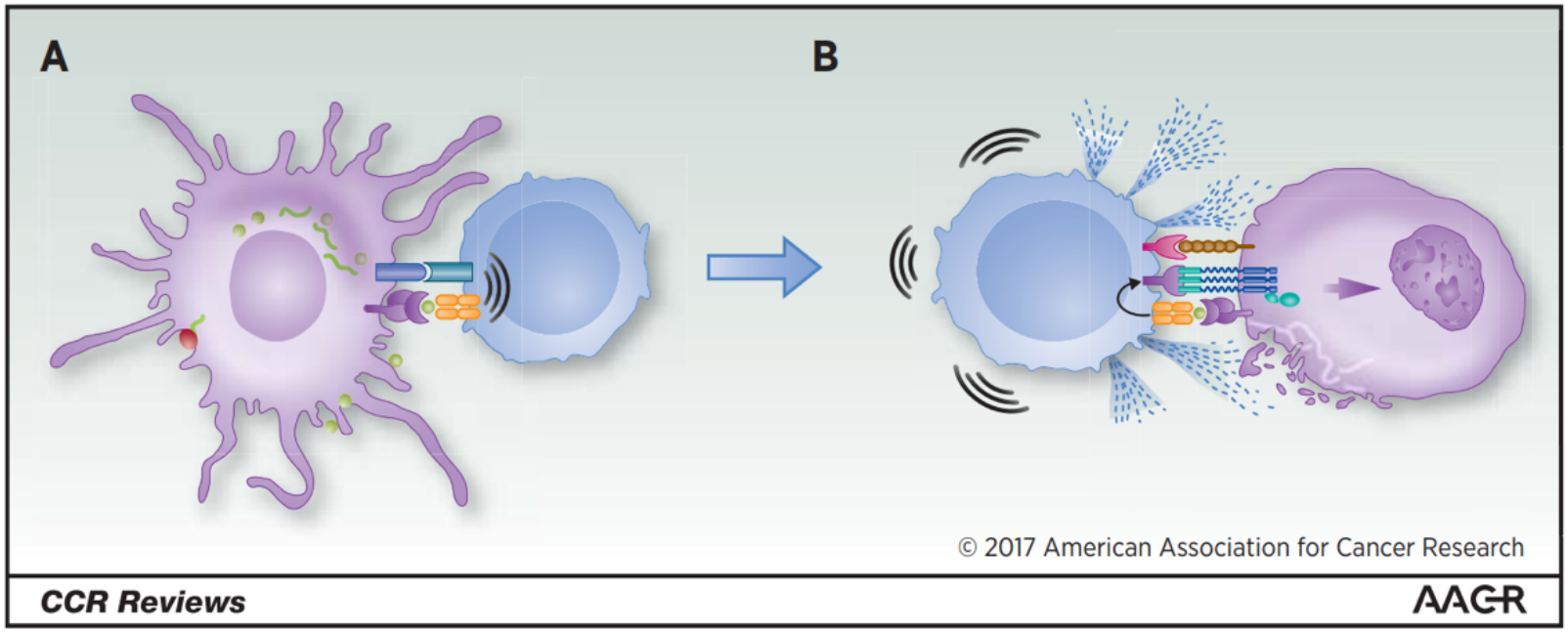
Requirements for Effective Immunotherapy

Initiation **Facilitation**



Vaccine (brachyury)
IL-15 (NK and T-cells)

PD-L1
TGF-beta
IDO

Bilusic M, Madan RA, Gulley JL *Clin Ca Res* 2017

Brachyury Makes Cancer Cells Behave Badly

- Transcription Factor Important in Embryogenesis
  - Master Driver of Metastatic Process (EMT)
  - Involved in Drug Resistance
  - Associated with Stem-like Properties

Brachyury in Prostate Cancer

Clinical Cancer Research

Biology of Human Tumors

T-box Transcription Factor Brachyury Is Associated with Prostate Cancer Progression and Aggressiveness

Filipe Pinto[1,2], Nelma Pértega-Gomes[1,2], Márcia S. Pereira[1,2], José R. Vizcaíno[3], Pedro Monteiro[4], Rui M. Henrique[5,6,7], Fátima Baltazar[1,2], Raquel P. Andrade[1,2], and Rui M. Reis[1,2,8]

Overexpressed in cancer vs. normal (protein and mRNA)
Correlates with aggressive tumors, invasion

Nov 2017

Cancer Therapy: Clinical

Clinical Cancer Research

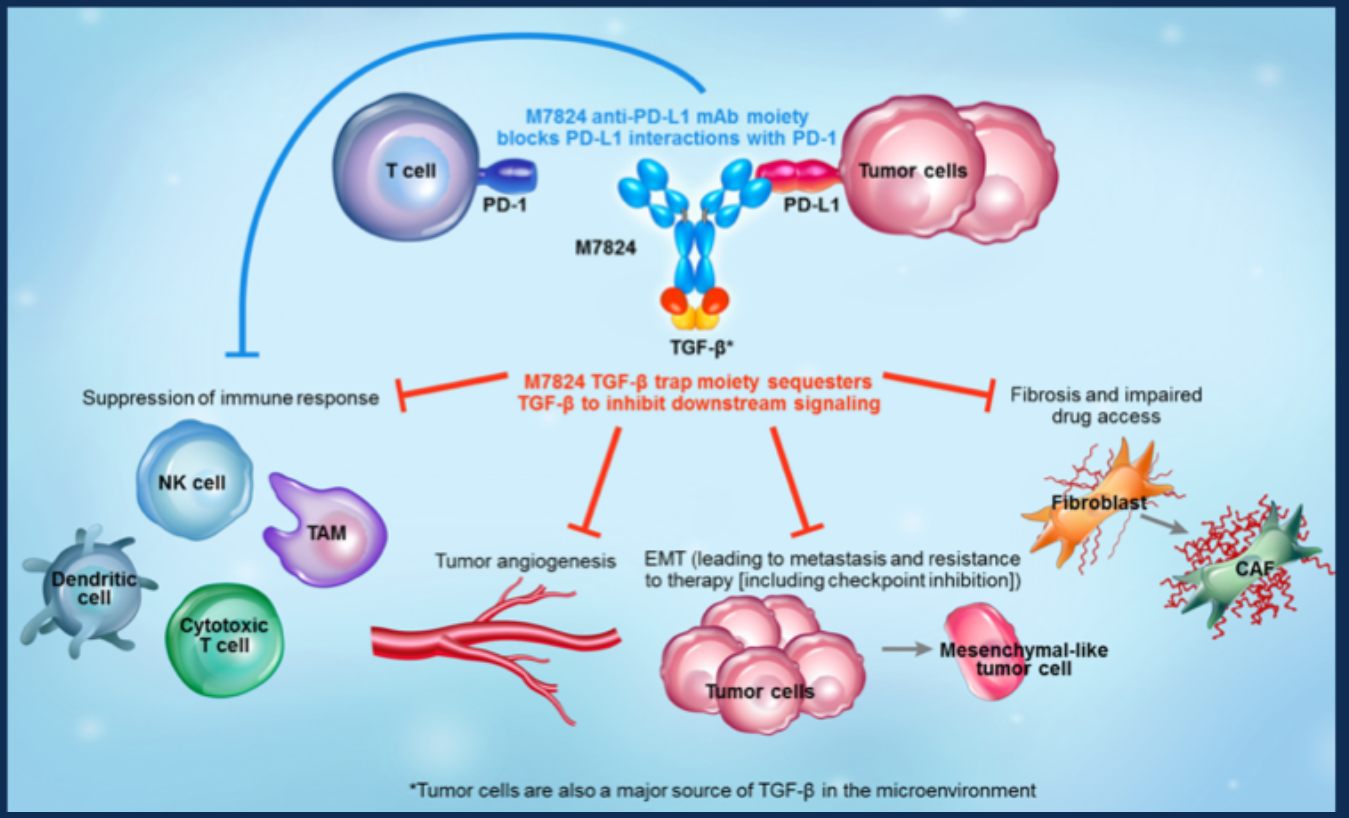
Phase I Study of a Poxviral TRICOM-Based Vaccine Directed Against the Transcription Factor Brachyury

Christopher R. Heery[1], Claudia Palena[1], Sheri McMahon[2], Renee N. Donahue[1], Lauren M. Lepone[1], Italia Grenga[1], Ulrike Dirmeier[3], Lisa Cordes[2], Jenn Marté[2], William Dahut[2], Harpreet Singh[2], Ravi A. Madan[2], Romaine I. Fernando[1], Duane H. Hamilton[1], Jeffrey Schlom[1], and James L. Gulley[2]

- Well tolerated (no DLT)
- 28 of 34 (82%) patients developed brachyury-specific CD4 and/or CD8 T-cell responses after vaccination

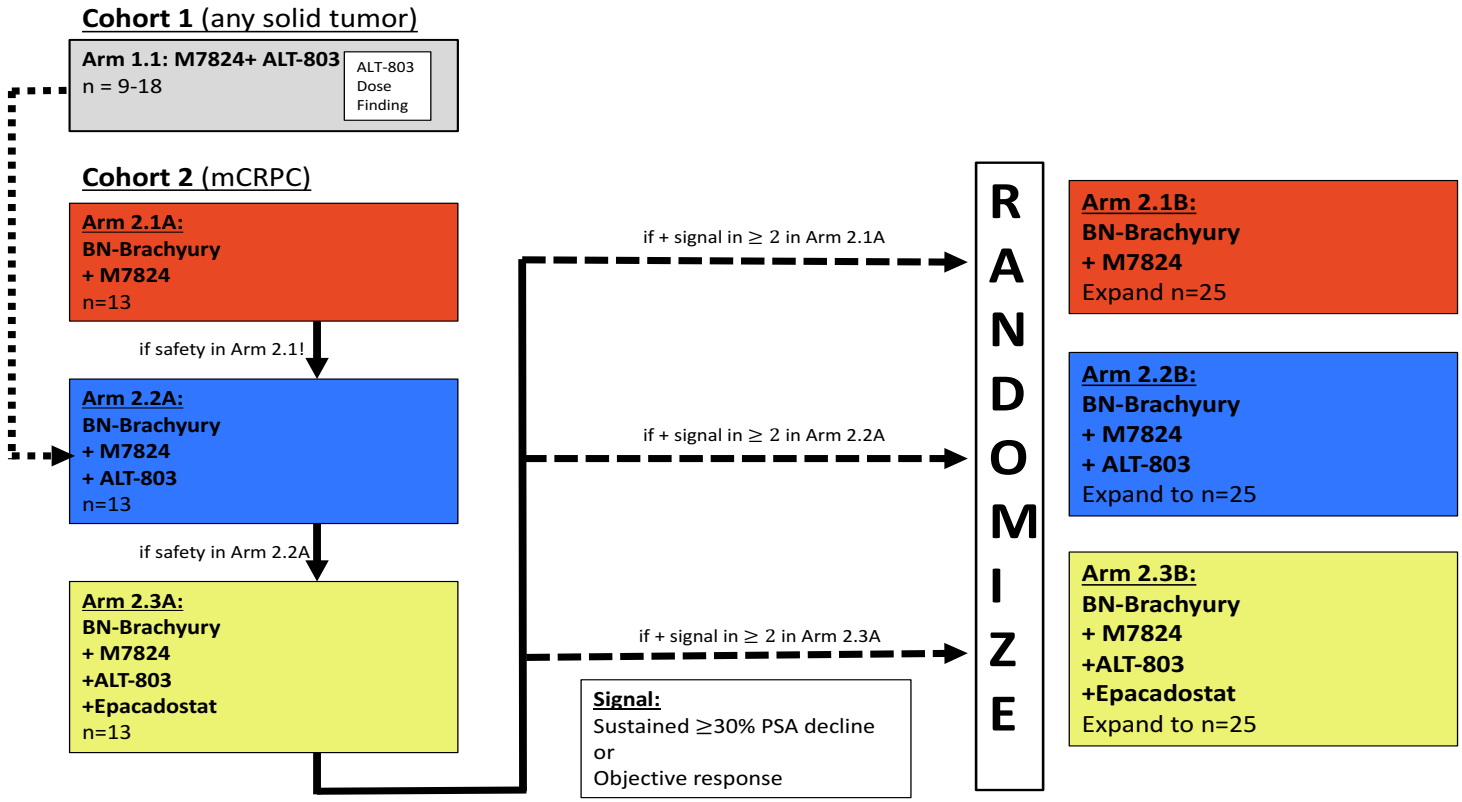
M7824

- M7824 is an innovative first-in-class bifunctional fusion protein
- Phase I dose escalation data presented at ASCO 2017
  - n=19
  - Well tolerated
  - Sequesters all activated TGF-beta in plasma throughout dosing period
  - Promising clinical activity
    - 1 CR
    - 3 PRs

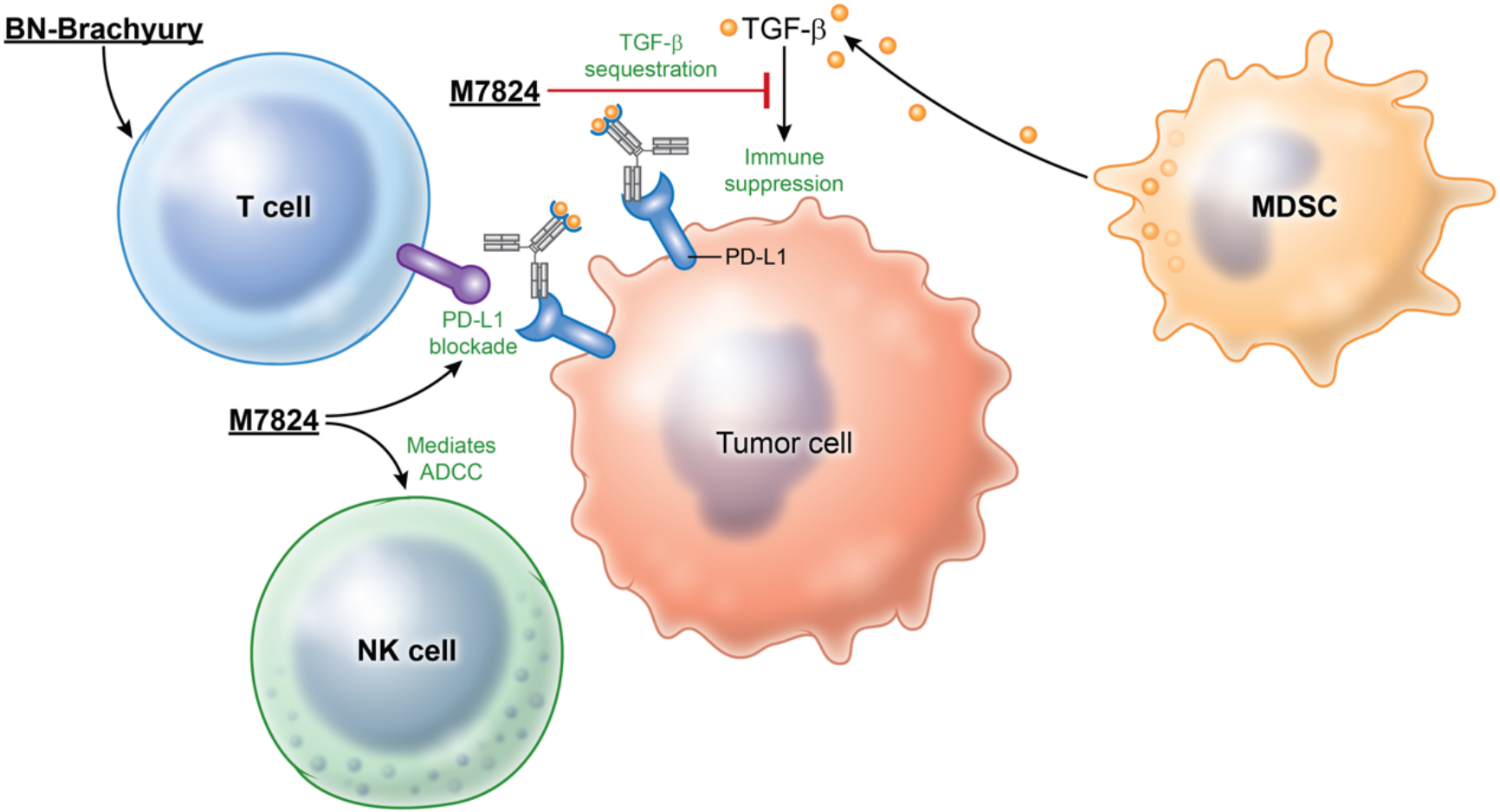


Clin Ca Res in press

QuEST (Quick Efficacy Seeking Trial)*



*NCI sponsored trial in review, FDA "May Proceed" last Friday (19 Jan 2018)


BN-Brachyury
T cell
M7824
TGF-β sequestration
TGF-β
Immune suppression
MDSC
PD-L1
PD-L1 blockade
M7824
Mediates ADCC
Tumor cell
NK cell

Conclusions

- T-cell poor tumors may require a “spark” to get the immune system to recognize and seek to destroy the tumor.
  - One of the most efficient ways of doing this is with vaccine
  - Sipuleucel-T is approved in the US
- There are some MSI hi prostate cancers (2-10% of mCRPC) that may respond to PD-1/PDL-1 inhibition (MSI testing)
- The tumor immunity cycle is an ongoing iterative process that may lead to an individualized evolution of the immune response to focus on targets most immunologically relevant for a given patient (e.g., neoantigens) (#PrecisionMedicine #PersonalizedMedicine #ImmuneSculpting)
- Approaches that both steer the immune system (e.g., vaccine) and allow effector cells to get to and remain functional within the TME (e.g., immune checkpoint blockade) will be optimal
  - Ongoing trials should help determine the utility of this approach